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A simple two-step synthesis of 2-(alkylamino)-1-arylethanols, including racemic adrenaline, from aromatic aldehydes via 5-aryloxazolidines

Vladimir S. Moshkin *, Vyacheslav Ya. Sosnovskikh

Department of Chemistry, Ural Federal University, prosp. Lenina 51, 620000 Ekaterinburg, Russia

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ABSTRACT

Benzaldehydes react smoothly with nonstabilized azomethine ylides, generated in situ from sarcosine/formaldehyde or *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, to give 5-aryloxazolidines as intermediates. These were converted into 2-(alkylamino)-1-arylethanols in good yields by simple heating in methanol with hydrochloric acid, or by treatment with hydrazine hydrate in ethanol.

The chemistry of β-hydroxy-β-phenethylamines has attracted considerable attention from the synthetic community due to their wide distribution in Nature and various biological activities.[1] Examples of such compounds include the alkaloids halostochine (**1a**), longimammine (**1b**), and normacromerine (**1c**), as well as the drugs phenylephrine (**1d**) and epinephrine (**1e**) (Fig. 1).[2] The latter, also known as adrenaline, 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol, is a naturally occurring hormone and a neurotransmitter, which has many functions in the body, regulating heart rate, blood vessel and air passage diameters. It has many clinical uses due to its potent actions on the heart, and on vascular and other smooth muscles; it also acts as a cardiac stimulant and has effects on gastrointestinal, uterine, and bronchial muscles.[3]

Due to the important applications of this class of compounds, their synthesis has been studied extensively.[4] Most pertinent to the present research are the reactions involving the oxazolidine system as a starting material. To the best of our knowledge, there are only two related examples reported in the literature. In 1970, Rizzi investigated the reaction of benzaldehyde and *m*-benzyloxybenzaldehyde with sarcosine and obtained diaryloxazolidines, which were subsequently hydrolyzed with hydrochloric acid to form halostochine (**1a**) and debenzylated into phenylephrine (**1d**) in low yields.[5] Later, Orsini found that the intermediate unsymmetrical nonstabilized azomethine ylides generated from sarcosine and aromatic aldehydes reacted with a second molecule of aldehyde to produce a mixture of regioisomeric diaryloxazolidines, which resulted in low yields during the Rizzi synthesis.[6]

In connection with our interest in azomethine ylide chemistry,[7] we have developed convenient methods for the preparation of 1,2,3,4-tetrahydroisoquinolin-4-ols **3**, *N*-benzyl-β-hydroxy-β-phenethylamines **4**, and 4-aryl-1,2,3,4-tetrahydroisoquinolines **5**

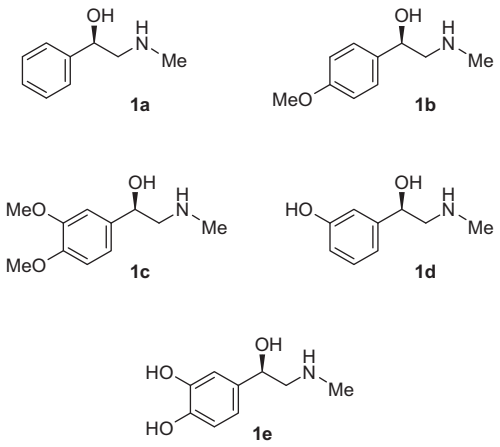

Figure 1. Examples of valuable 1-aryl-2-(methylamino)ethanols.

* Corresponding author. Fax: +7 343 261 59 78.
E-mail address: mvslc@mail.ru (V.S. Moshkin).

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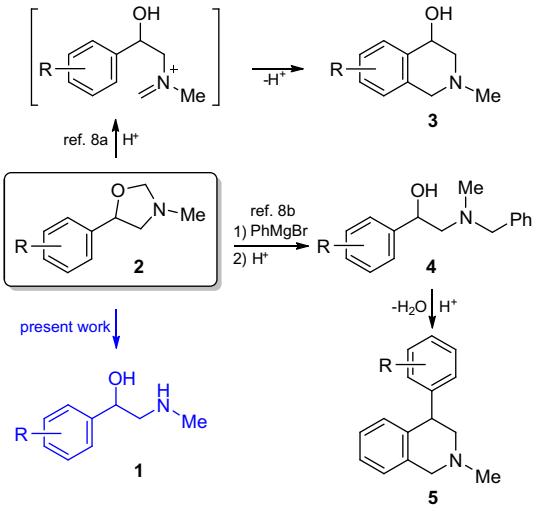
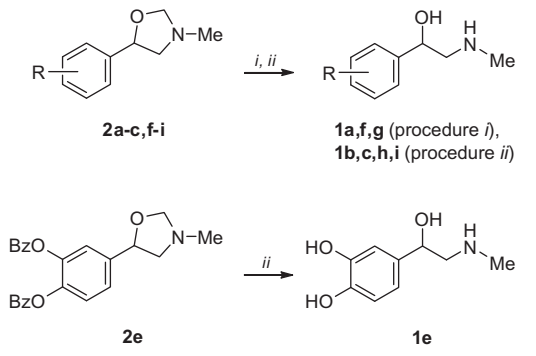
from aromatic aldehydes and an azomethine ylide derived from sarcosine and formaldehyde, via intermediate 5-aryloxazolidines **2**.[8] Taking into account these results, we envisaged that the ring-opening of oxazolidines **2** by removing the semi-aminal methylene group would produce the corresponding 1-aryl-2-(methylamino)ethanols **1**, and may provide a general and simple route for the synthesis of these important amino alcohols. To the best of our knowledge, no such approach has been reported previously (Scheme 1).

To test the feasibility of this idea, the reaction of 3-methyl-5-phenyloxazolidine (**2a**, R = H), obtained from benzaldehyde, sarcosine, and paraformaldehyde, with methanol was first investigated. We found that refluxing **2a**, methanol, and concentrated HCl (1.2 equiv) for 1.5 h resulted in the formation of desired halostachine (**1a**) in 61% overall yield, based on the starting aromatic aldehyde.[9] Using this approach, we were also able to obtain 1-(4-bromophenyl)-2-(methylamino)ethanol (**1f**) and 2-(methylamino)-1-(4-nitrophenyl)ethanol (**1g**) from the corresponding benzaldehydes in 59% and 63% yields, respectively (Scheme 2, Table 1). It should be noted that this reaction does not require any chromatographic purification of the intermediate liquid oxazolidines **2** or the products **1**, and thereby greatly facilitates the preparation of the target arylethanolamines. However, anisaldehyde, under the same conditions, gave a mixture of products, presumably due to the high nucleophilicity of the benzene ring and the stabilizing effect of the *p*-methoxy group on the benzylic carbocation intermediate, which facilitate intermolecular side reactions.

This problem can be overcome by using a previously reported demethylenation protocol on the oxazolidine ring with hydrazine hydrate in ethanol.[10] To our delight, this procedure gave longimammine (**1b**) in 70% yield from the starting anisaldehyde; normacromerine (**1c**) was obtained from veratraldehyde in a similar way in 59% yield. Analogous reactions with 2,4-dimethoxybenzal-



Scheme 1. One-pot syntheses of phenethylamine derivatives.



Scheme 2. Synthesis of β-hydroxy-β-phenethylamines **1**. Reaction conditions: (i) MeOH, HCl, reflux, 1.5 h; (ii) EtOH, $N_2H_4{\cdot}H_2O$, rt (2 d), reflux (3 h).

Table 1
Yields and melting points of β-hydroxy-β-phenethylamines **1**

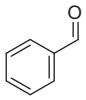
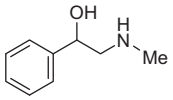
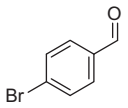
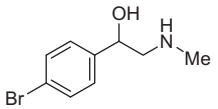
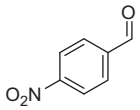
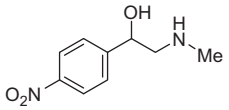
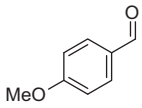
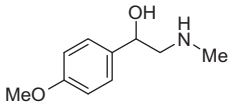
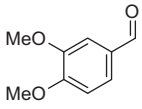
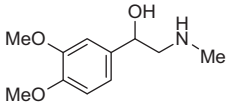
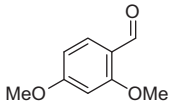
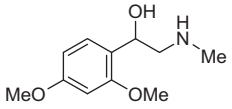
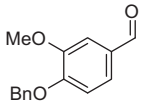
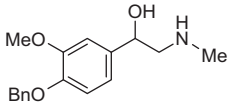
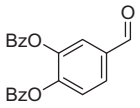
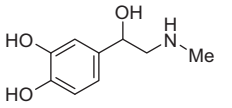
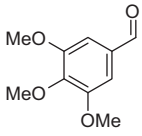
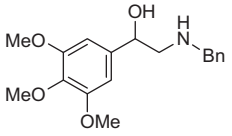
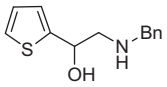
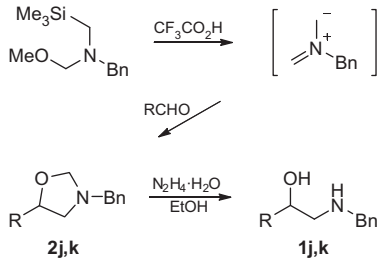
Aromatic aldehyde	β-Hydroxy-β-phenethylamine	Yield[a] (%)	Mp[b] (°C)
	 **1a**	61	75–77[c]
	 **1f**	59	93–95[d]
	 **1g**	63	115–117[e]
	 **1b**	70	103–105[f]
	 **1c**	59	100–103[g]
	 **1h**	49	79–82
	 **1i**	78	107–110
	 **1e**	67	210–213[h]
	 **1j**	68[i]	193–195[i]

Table 1 (*continued*)

Aromatic aldehyde	β-Hydroxy-β-phenethylamine	Yield[a] (%)	Mp[b] (°C)
		71	96–98[j]
	1k		

[a] Overall yield of phenylethylamine based on the starting aromatic aldehyde.
[b] Melting points are uncorrected.
[c] Mp 75.5–76.5 °C,[5] mp 71–74 °C.[13]
[d] Mp 91.5–93.7 °C.[14]
[e] Mp 117 °C,[15] mp 95–98 °C.[16]
[f] Mp 106–107 °C.[17]
[g] Mp 105–106 °C,[19] mp 107–108.5 °C.[2c]
[h] Mp 211–212 °C.[18]
[i] Yield and mp of the hydrochloride.
[j] Mp 84–85 °C.[20]



Scheme 3. Synthesis of compounds **1j**,**k**.

dehyde and 4-benzyloxy-3-methoxybenzaldehyde resulted in the formation of previously unknown β-hydroxy-β-phenethylamines **1h** and **1i**.[11] Finally, epinephrine (**1e**) was synthesized from 3,4-dibenzoyloxybenzaldehyde in 67% yield. In this case, the benzoyl protection was removed simultaneously by demethylenation of oxazolidine **2e** under the action of hydrazine hydrate (Scheme 2, Table 1).

An alternative method for the generation of a nonstabilized azomethine ylide from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine in the presence of trifluoroacetic acid,[12] followed by hydrazinolysis of oxazolidine **2j** allowed us to obtain *N*-benzyl derivative **1j** isolated as the hydrochloride. Application of this reaction to thiophene-2-carbaldehyde led to a two-step synthesis of 2-(benzylamino)-1-(thien-2-yl)ethanol (**1k**) in 71% yield (Scheme 3).

In conclusion, we have developed a practical, two-step route to *N*-alkyl-β-hydroxy-β-phenethylamines from aromatic aldehydes via a 5-aryloxazolidine intermediate, followed by its demethylenation. This one-pot synthesis can be considered as a formal *C*-nucleophilic addition of the methyl(benzyl)aminomethyl anion[21] from sarcosine/formaldehyde or *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine to the aldehyde carbonyl group. The proposed method allows easy access to biologically important phenethylamine derivatives. Further studies on this reaction are underway in our laboratory and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.083.

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8. (a) Moshkin, V. S.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 2455–2457; (b) Moshkin, V. S.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 2699–2702.
9. *General procedures for the preparation of 2-(alkylamino)-1-arylethanols* ***1a–c,f–i***. A mixture of the corresponding aromatic aldehyde (1.0 mmol), finely ground sarcosine (0.13 g, 1.5 mmol), and paraformaldehyde (0.09 g, 3.0 mmol) was refluxed in dry benzene (3.3 mL), with magnetic stirring and removal of formed water by means of a Dean–Stark trap, for 6–8 h. The resulting solution was evaporated in vacuo to give the oily 5-aryl-3-methyloxazolidines ***2a–c,f–i***, which were used without additional purification.
For the preparation of amino alcohols ***1a,f,g****:* the corresponding oily oxazolidine **2** was dissolved in MeOH (1 mL) and treated with concentrated HCl (0.10 mL, 1.2 mmol). The resulting mixture was refluxed in a fume hood with partial evaporation of the solvent for 1.5 h (for the removing of dimethoxymethane). The MeOH was evaporated in vacuo and H_2O (0.5 mL) was added. The mixture was extracted with Et_2O (2 × 1 mL) followed by basification with an excess of a cold concentrated solution of NaOH. Extraction with CH_2Cl_2 (2 × 2 mL), drying over Na_2SO_4, and evaporation gave the crude 1-aryl-2-(methylamino)ethanol, which was recrystallized from CH_2Cl_2–heptane mixture.
For the preparation of amino alcohols ***1b,c,h,i****:* the corresponding oily oxazolidine **2** was dissolved in EtOH (1 mL) and treated with hydrazine hydrate (0.4 mL). The resulting mixture was left at room temperature for 2 d and then refluxed for 3 h. The solvents were evaporated in vacuo and a concentrated aqueous solution of NaOH was added to the residue. Extraction with CH_2Cl_2 (2 × 2 mL), drying over Na_2SO_4, and evaporation gave the crude 1-aryl-2-(methylamino)ethanol, which was recrystallized from CH_2Cl_2–heptane mixture.
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11. *1-(2,4-Dimethoxyphenyl)-2-(methylamino)ethanol (****1h****)*. Colorless crystals, yield 49%, mp 79–82 °C (heptane–CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H, MeN), 2.42 (dd, J = 11.9, 8.5 Hz, 1H, CHH), 2.54 (dd, J = 11.9, 3.1 Hz, 1H, CHH), 3.74 (s, 3H, MeO), 3.75 (s, 3H, MeO), 4.88 (dd, J = 8.5, 3.1 Hz, 1H, CH), 6.47–6.52 (m, 2H, ArH), 7.26–7.30 (m, 1H, ArH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 35.9, 55.1, 55.3, 58.6, 65.1, 97.9, 104.5, 124.7, 127.0, 156.6, 159.3. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.76; H, 7.88; N, 6.67.
*1-[4-(Benzyloxy)-3-methoxyphenyl]-2-(methylamino)ethanol (****1i****)*. Colorless crystals, yield 78%, mp 107–110 °C (heptane–CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H, MeN), 2.56 (dd, J = 12.0, 4.8 Hz, 1H, CHH), 2.61 (dd, J = 12.0, 7.6 Hz, 1H, CHH), 3.77 (s, 3H, MeO), 4.59 (dd, J = 7.6, 4.8 Hz, 1H, CH), 5.05 (s, 2H, CH_2O), 6.83 (dd, J = 8.2, 1.5 Hz, 1H, H-6), 6.96 (d, J = 8.2 Hz, 1H, H-5), 6.98 (d, J = 1.5 Hz, 1H, H-2), 7.32 (t, J = 7.1 Hz, 1H, Ph), 7.39 (t, J = 7.1 Hz, 2H, Ph), 7.44 (d, J = 7.1 Hz, 2H, Ph); ^{13}C NMR (101 MHz, DMSO-d_6) δ 35.8, 55.5, 59.7, 70.0, 70.8, 110.1, 113.4, 117.9, 127.68, 127.74, 128.4, 137.4, 137.7, 146.7, 148.9. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.67; H, 7.43; N, 4.99.
*2-Benzylamino-1-(3,4,5-trimethoxyphenyl)ethanol hydrochloride (****1j****)*. Colorless crystals, yield 68%, mp 193–195 °C (i-PrOH). ^{1}H NMR (400 MHz, D_2O) δ 3.30 (dd, J = 13.0, 8.8 Hz, 1H, CHH), 3.36 (dd, J = 13.0, 3.7 Hz, 1H, CHH), 3.81 (s, 3H,

MeO), 3.89 (s, 6H, 2MeO), 4.35 (s, 2H, CH_2N), 5.06 (dd, J = 8.8, 3.7 Hz, 1H, CH), 6.78 (s, 2H, H-2, H-6), 7.49–7.55 (m, 5H, Ph); ^{13}C NMR (101 MHz, D_2O) δ 53.5, 54.7, 58.6, 63.4, 71.3, 105.7, 131.8, 132.3, 132.4, 132.8, 138.9, 139.0, 155.2. Anal. Calcd for $C_{18}H_{24}ClNO_4$: C, 61.10; H, 6.84; N, 3.96. Found: C, 61.18; H, 7.09; N, 3.99.

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